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REMARKS

At the outset, Applicant's attorneys wish to express appreciation for the courtesies extended by Examiners Dr. Elizabeth Kemmerer, Dr. Yvonne Eyler, and Dr. Gary Kunz during the January 6, 2004 interview. The inventor, Dr. James P. Elia; Assignee's representative, Dr. Jerry W. Bains; and Applicant's attorneys, Charles N. Lovell and Gerald K. White, attended the interview.

Applicant's attorney acknowledges receipt of the Examiner Interview Summary Record prepared by Examiner Kemmerer on January 6, 2004. Applicant believes that the Examiner's summary is accurate.

The restriction requirement of August 20, 2003 was traversed by Applicant and made FINAL by the Examiner. The Examiner then withdrew claims 6-203, 206-235, and 240-242 from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a non-elected invention, there being no allowable generic or linking claim. Claim 236 is a generic claim.

The Examiner kindly provided a listing of papers received from Applicant that are of record in the instant application. Applicant reviewed such listing and determined that the following papers appear to be missing from the Examiner's file; namely, Information Disclosure Statement filed on May 17, 2001; and Supplemental Information Disclosure Statement filed on March 18, 2003. A copy of these papers is enclosed with the instant Amendment. It is respectfully requested that the Examiner consider these papers and make them of record. Applicant appreciates the Examiner's diligence in ensuring that the record is complete.

Please note that claim 236 was amended to include that a new artery is formed by the process of the invention. Basis for such claim amendment may be found at page 46, lines 3-6 of the specification. As will be seen from the discussion of the obviousness rejection in a later

portion of this paper, Applicant respectfully believes that such amendment further distinguishes the claimed invention from the disclosure of Murry et al.

Claims 245, 248, and 249 stand rejected under 35 U.S.C. 112, first paragraph, as containing new matter. Specifically, the Examiner did not find descriptive support in the application as filed for the terms “multifactorial and non-specific cells”, “intravenous injection of cells”, “intraluminal injection of cells”, and “angioplasty delivery of cells”.

Regarding the term “multifactorial and non-specific cells” (claim 245), Applicant respectfully directs the Examiner’s attention to page 21, lines 14 and 15 and to page 37, line 19 of the instant specification. It is clearly disclosed, at page 21, lines 14 and 15, that growth factors can be multifactorial and non-specific and that the complete term “multifactorial and non-specific cells” is set forth at page 37, line 19. Thus, such term does not constitute new matter.

The Examiner further posits that the specification as filed does not provide antecedent support for delivering cells into a patient intravenously (claim 248), intraluminally (claim 249), or via angioplasty techniques (claims 252). The specification, at page 45, clearly describes injecting growth factors, e.g., genes, “into a patient intravenously, intraluminally or intramuscularly to promote the growth of a new artery. Or, the genes (or other genetic material) can be applied with an angioplasty balloon ...”. Growth factors contemplated by the invention are described in the specification as including genes and living organisms (genetic material) such as stem and germinal cells or any host cell.

It is not necessary to literally describe the subject matter of the claims in order to comply with the description requirement. Please see MPEP Section 2163.02 in this regard. All that is required is that the claims describe an invention that is clearly conveyed to one skilled in the art at the time the application was filed.

An objective standard employed by the courts in determining compliance with the description requirement of the statute is, “does the description clearly allow persons of ordinary skill in the art to recognize that ... [Applicant] invented what is claimed”. In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ 2d 1614, 1618 (Fed. Cir. 1989). Applicant submits that one skilled in the art reading the instant disclosure would reasonably understand that he was in possession of the novel concept of delivering cellular growth factors into a human patient intravenously, intraluminally, or via angioplasty to form a new artery as called for in the instant claims, cf. Vas v. Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ 2d 1111, 1117 (Fed. Cir. 1991). Applicant submits that the subject matter of claims 245, 248, and 249 is thereby supported by the disclosure of the instant application as filed under current law.

Claims 248 and 249 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enabling requirement. Basically, the Examiner considered that the description in Applicant’s specification would not enable one skilled in the art to practice a method of administering cells to a human patient via intravenous or intraluminal injection to cause growth of new muscle (and new artery) in the patient’s heart. The Examiner then cited eight factual determinations enumerated in In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988) and discussed each in support of the rejection for lack of enablement. Applicant respectfully disagrees with the Examiner’s position that the instant specification fails to satisfy the enablement requirement of the statute for the reasons set forth below.

First, the Examiner is respectfully referred to the concurrently filed Supplemental Declarations of Richard Heuser, M.D. and Andrew E. Lorincz, M.D. These highly qualified medical experts opine that, from reading the specification at page 20, line 10 through page 21, line 15 and page 44, line 19 through page 46, line 16, one skilled in the medical arts would be able to practice the invention set forth in all of the newly submitted claims (including claims 248

and 249 which specify intravenous and intraluminal injection) without need for resorting to undue experimentation. Please note that the terms “intravenous” and “intraluminal” are contained in the above-mentioned disclosure at page 45, lines 13-16 where various placement techniques are described. Each of the two declarants, despite having different medical backgrounds, opined that one skilled in the medical arts, armed with the knowledge contained in the instant application, would be able to practice the claimed invention without need for resorting to undue experimentation. Applicant considers that such expert opinions constitute strong evidence that undue experimentation would not be required to practice the invention set forth in claims 248 and 249; and, accordingly, the Examiner is requested to favorably reconsider the outstanding enablement rejection, cf. In re Alton, 76 F.3d 1168, 1174, 37 USPQ 2d 1578, 1583 (Fed.Cir. 1996).

Second, the Examiner’s attention is respectfully directed to publications authored by Strauer et al. and Deb et al. The Strauer et al. publication is of record and is included in Exhibit E of the previously submitted Declarations of Dr. Heuser and Dr. Lorincz. Another copy of the Strauer et al. publication is attached as Exhibit I of this Amendment for the convenience of the Examiner. A copy of the Deb et al. publication is attached as Exhibit II of this Amendment.

While the above-mentioned publications, as well as the publications cited in the later discussed obviousness rejection, speak for themselves, Applicant, for the convenience of the Examiner, has identified certain passages from such publications that Applicant submits support its position.

Strauer et al. discloses a form of intraluminal injection of cells into a heart artery. In this regard, please note that the last sentence of the abstract on the top of page 1913 states as follows:

These results demonstrate for the first time that selective intracoronary transplantation of autologous mononuclear BMCs is safe and seems to

be effective under clinical conditions. The marked therapeutic effect may be attributed to BMC-associated myocardial regeneration and revascularization.

Such intraluminal injection results in new artery growth and new muscle growth. Intraluminal injection is a well-known technique that was available prior to the filing date of this application and involves no special procedures or treatments to achieve the specified results. Instead, the cells were merely placed in the interior of the artery and then permitted to migrate to the heart of the patient where such claimed new growth occurs. Strauer et al. thus provides compelling evidence that nothing more than a routine intraluminal injection regimen is effective to achieve the inventive results of the invention. Moreover, it is clear that extensive experimentation is not required to practice the disclosed invention.

Deb et al., in a publication associated with the Mayo Clinic, reported an autopsy analysis of bone marrow cell transplant trials as follows:

These data establish for the first time human bone marrow as a source of extracardiac progenitor cells capable of de novo cardiomyocyte formation.

Official notice may be taken that bone marrow transplants are administered through intravenous injection (a specie of intraluminal injection) and have been used in the medical arts for a considerable time. In any event, the enclosed Exhibit III from the National Institute of Health's ("NIH") "Medical Encyclopedia: Bone Marrow Transplant" verifies such fact in the following passage at the top of page 2.

Bone marrow is taken from the donor in the operating room while the patient is unconscious and pain-free (under general anesthesia). Some of the bone marrow is removed from the top of the hip bone. The bone marrow is filtered, treated, and transplanted immediately or frozen and stored for later use. Then, transplant material is transfused into the patient through a vein (IV line) and is

naturally transported back into the bone cavities
where it grows to replace the old bone marrow.

Thus, little, if any, experimentation is required to use such common administration technique. Applicant believes that it is highly significant that the cells migrate to the human patient's heart without special procedures or treatments. Rather, the cells are intravenously administered and naturally migrate to the heart.

Applicant respectfully disagrees that the specification fails to satisfy the enablement requirement of the statute. Lest there be any doubt that the specification somehow does not teach a worker skilled in the medical arts how to use intravenous and intraluminal injections in the manner claimed by Applicant in claims 248 and 249, such doubt should be more than satisfied when the specification disclosure is coupled with the teachings in the Strauer et al. and Deb et al. publications. Obviously, the claimed invention is operative as described; and thus, enablement is present.

Applicant believes that the above-mentioned Strauer et al. and Deb et al. publications confirm that one skilled in the medical arts is enabled to practice the methods of claims 248 and 249 by merely following well-known administration techniques. Certainly, no more than routine experimentation, if any, would be required for such administration.

Third, although Applicant submits that the above-discussed evidence is of sufficient weight to rebut the Examiner's enablement rejection, the eight factual determinations enumerated in the In re Wands, 858 F.2d at 737, 8USPQ 2d at 1404, for making "undue experimentation" determinations are discussed below to fully respond to all of the points raised by Examiner.

As mentioned above, little, if any, experimentation would be required to practice the intravenous and intraluminal injection aspects of Applicant's invention. This point is confirmed

by the respective Supplemental Declarations of Dr. Heuser and Dr. Lorincz, as well as by the Strauer et al. and Deb et al. publications. Clearly, the use of simple, well-known administration techniques obtains the inventive results. The Examiner posits that a great amount of experimentation would be required to administer the cells at a site other than the heart and to cause such cells to adhere such that repair of the dead/damaged heart portion could be achieved. The above-mentioned Supplemental Declarations and publications clearly indicate that a great amount of experimentation is not required. Following administration of the cells, the body is believed to cause the cells to naturally migrate to the heart and to achieve the claims result, thus obviating the need for experiments such as described by the Examiner.

The comments made in the preceding paragraph also apply to the Examiner's point regarding the perceived need for additional "direction/guidance" regarding the types of delivery and need not be repeated.

The Examiner mentioned that no working examples were presented in the specification. As the Examiner is well aware, there is no legal or administrative requirement that a patent application must contain working examples. However, when operability or enablement issues arise during prosecution, as is the case here, it is incumbent upon Applicant to present evidence of operability or enablement in the form of actual data. The absence of examples may impact upon Applicant's burden of proof for overcoming the Examiner's *prima facie* case. In this instance, Applicant has proffered evidence in the form of the Strauer et al. and Deb et al. publications, which provide a strong showing of the invention's operability; and thus, the absence of working examples in the specification is of little or no weight.

The Examiner has described the nature of the invention as "extremely complex" and cited passages from Murry et al. as confirmation. Such passages relate to the problems associated with rapidity of heart damage and the consequent difficulty in limiting such damage. The

passages do not indicate complexity is involved with intravenous and intraluminal injection techniques in the context of new muscle and new artery growth in the heart. Although the problem of limiting heart damage in the several hours following a heart attack may be complex, Applicant is addressing the different problem of providing new muscle and new artery growth for a heart after damage has occurred rather than attempting to limit damage immediately following a heart attack. As may be seen from remarks presented above, the solution to Applicant's problem is believed to be rather simple and straightforward.

The Examiner indicated that the state of the art "indicates only localized injection of cells can successfully treat damaged myocardium" and then cites numerous publications in support of such point. Applicant does not agree that such publications are pertinent and all inclusive in defining the state of the art because none of the publications treat humans, and thus, any conclusions or inferences that are drawn from such publications are necessarily flawed. Moreover, the fact that the cited publications involve intramuscular injections directly into the myocardium does not automatically mean that such publications teach or suggest that other types of injection will not be operative. In any event, the Strauer et al. and Deb et al. publications are believed to demonstrate that the types of injection disclosed and claimed by Applicant, in addition to intramuscular injection, are effective for the treatment of human patients.

Applicant agrees with the Examiner that the level of skill in the art is high.

The Examiner also considered the art to be unpredictable because it could not be predicted if cells administered intravenously or intraluminally would reach the site of heart death/damage. Applicant believes that the facts involved in the instant application do not support the Examiner's statement that the art is unpredictable because Applicant has stated that intravenous and intraluminal injection would be effective types of administration and has then presented strong evidence to confirm such statement.

The Examiner considered the claims to be broad because no details of intravenous or intraluminal injection are recited. Applicant respectfully believes that no such details are required as the respective techniques are well-known in the art and do not involve specialized procedures or treatments to be effective. Dosages are not specified because Applicant believes that dosages need not be specified. Please see the concurrently submitted Supplemental Declarations of Dr. Heuser and Dr. Lorincz in this regard. Targeting molecules need not be specified for the invention to achieve its stated results. It is the human body that causes the cells to migrate naturally to the dead/damaged portion of the heart, and thus, the identity of a targeting molecule is not relevant. Applicant understands that the subject of targeting molecules is currently under study and that there appears to be a potential for such studies to result in a theoretical explanation of why Applicant's invention achieves the novel and unobvious results ascribed in the specification and claims. However, there is no requirement for Applicant to either explain the theory of the invention in the instant application or to make and disclose potential improvements thereof to provide an enabling disclosure of the claimed invention. Rather, Applicant's disclosure of the novel method and results, in and of themselves, constitutes an enabling disclosure of the claimed invention to one skilled in the art, thereby meeting the requirements of the patent statutes.

In view of the discussion presented above, Applicant submits, under the In re Wands test, that weighing all of the above noted factual determinations compels the conclusion that the instant specification satisfies the enablement requirement of the statute.

It is important to note that the first paragraph of the statute requires nothing more than objective enablement, and it is of no importance whether such teaching is set forth by use of illustrative examples or by broad terminology. As a general matter, an application disclosure which contains a teaching of how to make and use the invention in terms which correspond in

scope to those used in describing the invention sought to be patented is considered to be in compliance with the enabling requirement of the statute. In re Marzocchi, 58 CCPA 1069, 439 F.2d 220, 169 USPQ 367, 369-370 (1971). Further, “Section 112 does not require that a specification convince persons skilled in the art that the assertions therein are correct. In re Robins, 429 F.2d 452, 166 USPQ 552 (CCPA, 1970) *supra*”. [Emphasis added.]

In summary, Applicant submits that the evidence contained in the Supplemental Declarations of Dr. Heuser and Dr. Lorincz; the evidence contained in the Strauer et al. and Deb et al. publications; and the discussion of the eight points of In re Wands are sufficient to overcome the enablement rejection. The Examiner is thus requested to favorably reconsider the enablement rejection.

Claim 254 stands rejected for lacking the definiteness required under the second paragraph of 35 U.S.C. 112. Applicant respectfully disagrees that this claim lacks the requisite definiteness.

The Examiner posits that the terms “multifactorial and non-specific” are not clearly defined in the specification and that these terms are not commonly used to describe cells in the art but, rather, are used in a functional sense. The specification on page 37 specifically teaches that “multifactorial and non-specific cells (such as stem cells and germinal cells) can provide the necessary in vivo and in vitro cascade of genetic material.”

Thus, it is clear that Applicant used the questioned terms to define cellular material that can differentiate and possess homing/migration characteristics. One skilled in the art reading the invention defined in claim 254 in light of the instant specification would clearly understand the scope of protection provided thereby. Accordingly, the rejection under 35 U.S.C.112, second paragraph, must fail.

The Examiner, in the section of the Office Action entitled "Priority", noted that the application "appears to be virtually the same" as parent application 09/064,000 and fixed the effective date for the claimed invention as April 21, 1998, for purposes of applying prior art. The Examiner also stated that, "The instant application is also a continuation-in-part of 08/837,608, filed 21 April 1997; 08/326,857, filed 21 October 1994; 08/087,185, filed 02 July 1993; and 08/053,886, filed 27 April 1993."

However, the Examiner incorrectly concluded that "none of these applications have support for the currently claimed invention, i.e., administration of cells to repair dead or damaged heart tissue." Further, the Examiner mischaracterized the disclosures of the '886, '185, and '857 applications as being "limited to disclosures of dental implants and clearly do not provide support for treatment of non-dental tissues such as heart."

The disclosures found on pages 20 and 21 of the instant application describe using angiogenic growth factors comprising living organisms for growing soft tissue in a body, such as tissue of mesodermal origin, by injecting the growth factor at a selected site in a human patient. The growth factors are described as multifactorial and non-specific, i.e., characterized as being able to control cell growth, migration, and function. Such disclosure clearly conveys to one skilled in the art that Applicant was in possession of the novel method of using cellular angiogenic growth factors to grow mesodermal tissue, which include blood vessels, i.e., arteries in human patients. Further, pages 30 and 31 describe injecting a growth factor into the body to cause the body "to grow, reproduce and replace" skeletal tissue, i.e., an organ, or any desired soft tissue in the body, i.e., organ in the body. While it is true that the word "heart" does not appear, Applicant believes that one skilled in the art would understand that the heart, heart muscle, and blood vessels are comprised of soft tissue of mesodermal origin. Those skilled in the art reading such disclosure would understand that to "grow, reproduce and replace" soft tissue organs would

include using multifactorial and non-specific cellular growth factors to affect angiogenesis and growth of new tissue/organ of mesodermal origin, including arteries and muscle such as those found in the heart. Applicant believes that the aforesaid teachings evince possession of such novel concept as early as the July 2, 1993 filing date of the 08/087,185 application.

Applicant believes that the above-mentioned disclosures at pages 20, 21, 30 and 31 of the instant application, which correspond to disclosures carried forward from each of the parent applications in the chain of co-pending applications relied upon under 35 U.S.C. 120, teach the manner and process of making and using the invention which correspond in scope to the subject matter of the newly submitted claims and thusly satisfy both the description and enablement requirements of 35 U.S.C. 112. Accordingly, Applicant claims the benefit under 35 U.S.C. 120.

Claims 236-239, 243-247, 250, 251, and 253 stand rejected under 35 U.S.C. 103(a) in view of Murry et al. The Examiner essentially stated that Murry et al. responds to the claimed invention except for treating a rat rather than a human patient and then reached the legal conclusion that it would be obvious to treat a human patient. Applicant does not agree with either the Examiner's characterization of the disclosure of Murry et al. or with the above-mentioned legal conclusion of obviousness for several significant reasons. Amended claim 236 requires formation of a new artery, as well as new muscle, to more clearly define Applicant's contribution to the art. Basis for such claim amendment may be found at page 46, lines 3-6 of the specification. As more fully explained below, Murry et al. does not disclose the claimed results of growing a new artery; and it would not be obvious that the rat study of Murry et al. could be predictably used to treat a human patient to achieve such results.

Initially, Applicant submits that Murry et al. is not a competent statutory reference. As set forth earlier, Applicant claims the benefit under 35 U.S.C. 120 of a chain of co-pending applications beginning with Serial No. 08/087,185, filed on July 2, 1993, through the instant

application all of which applications are believed to satisfy the requirements proscribed by 35 U.S.C. 112 in regard to the subject matter sought to be patented in newly amended claims 236-239, 243-247, 250, 251, and 253. Accordingly, the Murry et al. article must fail as a prior art reference because it does not have a competent publication date.

Assuming, *arguendo*, that Murry et al. is somehow a competent reference against the claims of the instant application, Applicant now addresses the merits of the Murry et al. publication.

Prior to discussing the Murry et al. publication in detail, Applicant desires to address one aspect of the rejection. The Examiner interpreted the term “artery” in the claims as any blood vessel leading away from the heart and alleged that such is recognized in the art. The Examiner then further stated that Applicant’s specification does not provide an alternative definition for “artery” that excludes capillaries. Applicant respectfully believes that the above statements of the Examiner are incorrect. At page 44, lines 12 and 13 of the specification an organ is defined as “two or more kinds of tissues joined into one structure that has a certain task.” At page 45, line 1 of the specification it is stated that, “An artery is an organ from the circulatory system.” Thus, Applicant has defined an artery as having two or more kinds of tissue joined into one structure.

The World Book Encyclopedia, attached as Exhibit IV, defines an organ as “an organ consists of two or more kinds of tissue joined into one structure that has a certain task.” Such definition and Applicant’s definition are the same. An artery is an organ; therefore, at least two kinds of tissue must be present. Merriam-Webster’s MEDLINEplus Medical Dictionary, attached as Exhibit V, indicates that an artery includes a muscular component. A capillary is excluded from the definition of an artery because a capillary consists of a single layer of endothelium and has no muscular component. Please refer to page 395, last full paragraph of the

right column, of Encyclopedia Britannica, attached as Exhibit VI, in this regard. From the above remarks, it is clear that Applicant has always considered that an artery is a multiple tissue vessel and that a capillary is known in the medical arts as a single walled vessel. Obviously, the term “capillary” cannot be construed broadly to include an artery as postulated by the Examiner.

Turning to the rejection under 35 U.S.C. 103(a), Applicant believes that there are at least two significant differences between Murry et al. and the claimed invention. First, Murry et al. reported a capillary, not the claimed new artery. As explained above, a capillary is not an artery. Second, Murry et al. did not treat a human patient.

The Examiner considered that the rat system used by Murry et al. was clearly used as a model for human treatment and that a reasonable expectation of success for human treatment would be present. Murry et al. utilizes a murine model. Such model relates to the genus “mus” or to its subfamily (murinae) that includes most of the rats and mice that live in intimate association with humans. Applicant respectfully disagrees with the Examiner’s conclusion because a rat system simply is not a predictable human model and thus does not have a reasonable expectation of success or duplication for humans. Further, one following the teachings of Murry et al. would expect to obtain a capillary, not the claimed new artery. One of ordinary skill in the art would not be motivated to utilize the Murry et al. technique to grow a new artery in a human because no expectation of artery growth is present in the Murry et al. publication. Rather, a capillary was disclosed by Murry et al. Thus, predictability is absent.

Even more fundamentally, Murry et al., at page 2516 states that:

The skeletal myofibers of the graft do not express MHC-alpha, nor does the underlying scar tissue (wound). This indicates that the grafted skeletal muscle does not show cardiac differentiation.

Further, at page 2520 Murry et al. states that:

...the engrafted myoblasts initially proliferate and then begin to form multinucleated myotubes by day 3 ...

Murry et al. recognized that new cardiac muscle was not grown. Please see page 2521 where Murry et al. states the following:

More importantly, the grafted cells expressed skeletal muscle-specific proteins and failed to express the cardiac-specific isoform MHC-alpha up to 3 mo. after transplantation. Thus, there was clearly no cardiac differentiation in this study.

Applicant wishes to call the Examiner's attention to another publication regarding rat models authored by Hill et al. Maria Hill and co-author Professor Geoffrey Goldspink are affiliated with the Royal Free and University College Medical School at London, U.K. Co-author A. Wernig is affiliated with the Department of Physiology at the University of Bonn in Germany. Please see attached Exhibit VII in this regard. Hill et al. stated the following at page 1:

In post-mitotic tissues, damaged cells are not replaced by new cells and hence effective local tissue repair mechanisms are required. In skeletal muscle, which is a syncytium, additional nuclei are obtained from muscle satellite (stem) cells that multiply and then fuse with the damaged fibres.

In summary, both Murray et al. and Hill et al. used rat models and satellite (stem) cells and obtained fusion rather than new cells.

The results reported for non-human experiments were seriously questioned in a three-nation, five-university study funded by the NIH. Please see attached Exhibit VIII containing the Alvarez-Dolado et al. report at page 1 in this regard. Utilizing a murine model, Alvarez-Dolado et al. stated the following:

Recent studies have suggested that bone marrow cells possess a broad differentiation potential, being able to form new liver cells, cardiomyocytes and neurons. Several groups have attributed this apparent plasticity to 'transdifferentiation'. Others, however, have suggested that cell fusion could explain these results. Using a simple method based on Cre/lox recombination to detect cell fusion events, we demonstrate that bone-marrow-derived cells (BMDCs) fuse spontaneously with neural progenitors *in vitro*. Furthermore, bone marrow transplantation demonstrates that BMDCs fuse *in vivo* with hepatocytes in liver, Purkinje neurons in the brain and cardiac muscle in the heart, resulting in the formation of multinucleated cells. No evidence of transdifferentiation without fusion was observed in these tissues. These observations provide the first *in vivo* evidence for cell fusion of BMDCs with neurons and cardiomyocytes, raising the possibility that cell fusion may contribute to the development or maintenance of these key cell types.

Furthermore, proof that bone marrow cells form new cardiomyocytes in humans is provided in previously discussed Exhibit II authored by Deb et al. The Examiner's attention is directed to pages 1 and 2 of the Deb et al. publication where the following information appears:

Abstract

Background – Recent studies have identified cardiomyocytes of extracardiac origin in transplanted human hearts, but the exact origin of these myocyte progenitors is currently unknown.

Methods and Results – Hearts of female subjects (n=4) who had undergone sex-mismatched bone marrow transplantation (BMT) were recovered at autopsy and analyzed for the presence of Y chromosome-positive cardiomyocytes. Four female gender-matched BMT subjects served as controls. Fluorescence in situ hybridization (FISH) for the Y chromosome was performed on paraffin-embedded sections to identify cells of bone marrow origin with concomitant immunofluorescent labeling for – sarcomeric actin to identify cardiomyocytes. A total of 160 000 cardiomyocyte nuclei were

analyzed approximating 20 000 nuclei per patient. The mean percentage of Y chromosome-positive cardiomyocytes in patients with sex-mismatched BMT was $0.23 \pm 0.06\%$. Not a single Y chromosome-positive cardiomyocyte was identified in any of the control patients. Immunofluorescent costaining for laminin and chromosomal ploidy analysis with FISH showed no evidence of either pseudonuclei or cell fusion in any of the chimeric cardiac myocytes identified.

Conclusions – These data establish for the first time human bone marrow as a source of extracardiac progenitor cells capable of de novo cardiomyocyte formation.

Additional proof of bone marrow and peripheral blood cell differentiation in the formation of new cells in humans is provided in a publication of the NIH authored by Tran et al., attached as Exhibit IX. In this regard, please note the following information contained at page 1084 of Tran et al.:

BACKGROUND: Adult bone marrow-derived (BMD) cells could be used to repair damaged organs and tissues, but the intrinsic plasticity of these cells has been questioned by results of in-vitro studies suggesting that such cells might fuse with other cells giving the appearance of differentiation. We aimed to determine whether fusion events are important in vivo.

METHODS: To test whether BMD cells can colonise an epithelial tissue and differentiate there without fusion, we did in-situ hybridization with Y and X chromosome probes labeled with 35-sulphur or digoxigenin, or labeled fluorescently. We did immunohistochemistry with anticytokeratine 13 along with fluorescence in-situ hybridization to identify Y-chromosome positive buccal epithelial cells in cheek scrapings obtained from five females who had received either a bone-marrow transplant or an allogeneic mobilized peripheral-blood progenitor-cell transplant (enriched in CD34+ cells) from male donors.

FINDINGS: When examined 4-6 years after male-to-female marrow-cell transplantation, all female recipients had Y-chromosome-positive buccal cells (0.8-12.7%). In more than 9700 cells studied, we detected only one XXXY-positive cell (0.01%) and one XXY cell (0.001%), both of which could have arisen when an XY cell fused with an XX cell.

INTERPRETATION: Male BMD cells migrate into the cheek and differentiate into epithelial cells, an occurrence that does not depend on fusion of BMD cells to recipient cells. This finding might be an example of transdifferentiation of haemopoietic or stromal progenitor cells. Plasticity of BMD cells could be useful in regenerative medicine.

The above-discussed publications compel two conclusions; namely:

1. Murine models are not appropriate to predict human response because different results are obtained for rodents than for humans. Murine trials resulted in fusion while human trials resulted in new cell growth. Thus it appears that different repair mechanisms and respective treatment results are obtained. Hence, the requisite predictability would be absent; and
2. There are serious questions raised in the aforementioned three-nation, five-university NIH study of Alvarez-Dolado et al., attached as Exhibit VIII, regarding inconsistent reported results; and thus, animal studies, including murine studies, are not a reliable basis to predict the result of human studies.

In connection with the rejection of claim 253, the Examiner remarked that, "All cells comprise genes, and thus the stem cells administered by Murry et al. also comprise genes as

recited in claim 253." The Examiner further stated that claim 253 did not require the gene to be heterologous with respect to the cell.

Applicant does not agree with the Examiner's broad statement that all cells comprise genes. Mature red blood cells do not have a cell nucleus, nuclear genes, or mitochondria. Therefore, the statement that all cells comprise genes is not true. Regarding cellular growth factors, please note that an enucleated ovum is disclosed as a growth factor at page 52, line 26. Such material contains no nuclear genes (only mitochondrial DNA). Applicant, however, agrees with the Examiner that stem cells contain genes.

Applicant believes that claim 253 should be construed in a reasonably broad fashion that is consistent with the specification. In this regard, a combination of gene and cell treatments are disclosed at page 52, line 14 and page 61, lines 8-10; and insertion of a gene into a cell is described at page 48, lines 16-29; page 51, line 28 through page 52, line 3; and page 55, lines 5-9. Applicant submits that claim 253 should be construed in light of Applicant's specification where a combination of treatments, including gene insertion into a cell, are described rather than construing claim 253 in an impermissibly broad fashion to include naturally occurring cells containing genes. In view of the above remarks, it is clear that Applicant intended to, and in fact does, claim the use of a combination of two growth factor species in claim 253.

In any event, the patentability of claim 253 does not depend upon whether or not the Examiner agrees with Applicant's claim construction because claim 253 depends upon claim 236, a claim believed to contain patentable subject matter. Thus, claim 253 must also be considered to be patentable.

Please note that the claims have been amended to specify that new arteries are formed by the claimed method. This further distinction over Murry et al. underscores the fact that rat models achieve different results than humans. Accordingly, it is submitted that the human

results of the invention are unobvious to one of ordinary skill in the art. The Examiner is respectfully requested to withdraw the obviousness rejection based upon Murry et al.


Claims 252 stands rejected under 35 U.S.C. 103(a) as being unpatentable in view of Murry et al. as applied to claims 236-239, 243-247, 250, 251, and 253 above, and further in view of Nabel et al. Murry et al. was discussed extensively above, and such remarks are repeated herein. Nabel et al. relates to a known balloon catheter technique for administering cells for a different purpose than Applicant. Applicant believes that Nabel et al. cannot cure the deficiencies of Murry et al.; and hence, claim 252 is also drawn to unobvious subject matter.

For the above-mentioned reasons and supporting evidence, Applicant respectfully submits that that claims 236, 238, 239, and 243-253, insofar as such claims pertain to cellular growth factors, are in condition for allowance; and a notice to such effect is respectfully requested.

Should the Examiner have any questions or require additional information or discussion to place the application in condition for allowance, a phone call to the undersigned attorney would be appreciated.

Respectfully submitted,

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